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Influence of heart rate increase on uncorrected pre-ejection period/left ventricular ejection time (PEP/LVET) ratio in normal individuals

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In 26 normal volunteers, increase in heart rate from mean 73·94±1·97 to 103·61±2·72/min, by either intravenous atropine administration or rapid right atrial pacing, produced definite changes in the uncorrected systolic time intervals. As expected, total electromechanical systole (QS_2) and left ventricular ejection time (LVET) were shortened, while the pre-ejection period (PEP) was unaffected. There was a consistent and significant increase of the PEP/LVET ratio ($P<0·001$). It is postulated that when this ratio is taken to express left ventricular contractility, it should probably be corrected for heart rate. Appropriate regression equations for such a correction were calculated (PEP/LVET=0·249+0·0168 HR).

Measurement of the systolic time intervals of the left ventricle as reported by Weissler, Harris, and Schoenfeld (1968, 1969) is currently being applied widely for the evaluation of cardiac function. The advantages and reliability of this method, as well as reservations about its validity, have been already discussed in numerous publications (Aronow, Bowyer, and Kaplan, 1971; McConahay, Martin, and Cheitlin, 1972; Parker and Just, 1974). Weissler and co-workers (1969) have particularly stressed the use of the pre-ejection period/left ventricular ejection time (PEP/LVET) ratio as a very sensitive index of ventricular function. According to these investigators this ratio offers the additional advantage of being self-corrected for sex and heart rates from 50 to 110/min. Most authors have subsequently adhered to this principle, and have used the PEP/LVET ratio in its uncorrected form (McConahay *et al.*, 1972; Timmis *et al.*, 1975). However, it becomes apparent from Weissler's own regression equations and additional investigators' reports that the PEP and the external isovolumic contraction time (EICT) are only minimally affected by changes in heart rate (Goldstein, DeGroot, and Leonard, 1961; Harris, Schoenfeld, and Weissler, 1967; Talley, Meyer, and McNay, 1971), while the LVET is altered to a considerable degree (Wallace *et al.*, 1963). Therefore, changes in heart rate would be expected to yield a larger PEP/LVET ratio.

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We investigated whether correction of this ratio for heart rate is justified. Some authors have already corrected this ratio, using Weissler's equations (Strangfeld *et al.*, 1973; Frishman *et al.* 1975), but as far as we know no detailed data have been given on the behaviour of this ratio with heart rate changes.

Subjects and methods

Twenty-six subjects were included in this study. Most were house physicians, and hospital personnel. In two patients STI intervals were measured during the process of rapid right atrial pacing for the investigation of atypical chest pain (both tests proved negative). Ages ranged from 17 to 38 years (mean 27·1). All were considered free from any cardiac abnormality by history, clinical examination, resting and exercise electrocardiograms (submaximal test: 85% of predicted maximal heart rate), and evaluation of heart size and motion by image intensifier fluoroscopy. The electrocardiogram (usually lead II), carotid pulse tracing, and phonocardiogram were recorded on a Hewlett-Packard 4578A photographic multichannel recorder. Thus, the heart rate, total electromechanical systole (QS_2), and left ventricular ejection time (LVET) were

TABLE *Systolic time intervals before and after the production of tachycardia*

Case No.	Sex	Age (y)	I: Basal HR min	QS_2 (ms)	LVET (ms)	PEP (ms)	PEP/ LVET	PEP_I/ $LVET_I$	II: After tachycardia HR min	QS_2 (ms)	LVET (ms)	PEP (ms)	PEP/ LVET	PEP_I/ $LVET_I$
1	F	21	61·2	416·0	303·8	112·2	0·369	0·340	92·3	381·0	265·3	115·7	0·436	0·369
2	M	36	56·5	452·4	347·5	104·9	0·301	0·287	63·4	445·1	338·1	107·0	0·316	0·296
3	F	20	81·0	388·3	276·5	111·8	0·404	0·355	127·6	331·5	224·8	106·7	0·474	0·367
4	F	20	79·0	381·4	283·0	94·8	0·334	0·308	130·1	331·1	239·1	92·0	0·384	0·322
5	M	25	83·9	374·5	266·0	108·5	0·407	0·347	107·3	324·5	224·0	100·5	0·448	0·352
6	M	19	59·5	415·3	307·5	107·8	0·350	0·322	96·8	340·0	243·5	96·5	0·396	0·331
7	M	17	72·4	381·2	281·7	99·5	0·353	0·317	113·2	341·5	231·1	110·4	0·477	0·367
8	M	24	62·5	365·6	276·7	88·9	0·321	0·297	96·7	344·2	260·0	84·2	0·323	0·289
9	A	22	77·1	397·7	287·7	110·0	0·382	0·342	107·1	373·9	249·7	124·2	0·497	0·386
10	A	22	71·2	417·5	301·4	116·1	0·385	0·342	93·0	384·5	262·8	121·7	0·463	0·377
11	A	37	82·9	379·0	275·3	103·7	0·376	0·335	109·0	338·8	232·6	106·2	0·456	0·368
12	F	38	68·7	391·4	276·5	114·9	0·415	0·361	107·1	324·2	219·0	105·2	0·480	0·379
13	F	23	75·3	387·8	287·8	100·5	0·349	0·319	87·3	380·7	285·0	95·1	0·332	0·306
14	F	24	70·6	385·4	278·7	106·7	0·382	0·344	103·6	365·0	263·0	102·0	0·387	0·334
15	M	38	77·0	388·5	284·5	104·0	0·365	0·324	114·7	324·0	229·5	94·5	0·411	0·411
16	F	30	91·0	411·4	316·0	95·4	0·301	0·285	109·0	379·1	286·2	92·9	0·324	0·296
17	F	22	82·6	393·3	298·2	95·1	0·318	0·297	104·7	348·1	263·8	84·3	0·319	0·292
18	F	29	66·6	432·0	317·3	114·7	0·361	0·333	105·2	374·5	257·2	117·3	0·456	0·374
19	M	17	88·0	358·6	252·4	104·2	0·412	0·346	124·2	321·7	214·2	107·5	0·501	0·369
20	M	30	69·3	424·2	297·0	127·2	0·428	0·373	86·2	410·0	278·5	132·0	0·473	0·391
21	M	31	80·3	373·4	272·8	100·6	0·368	0·328	101·6	358·1	256·1	102·0	0·398	0·332
22	M	30	79·1	395·8	277·0	118·8	0·428	0·365	93·7	386·3	256·5	129·8	0·506	0·402
23	M	30	64·2	418·5	308·3	110·2	0·357	0·325	100·0	364·5	246·0	118·5	0·481	0·385
24	M (P)	30	93·7	361·5	259·5	102·0	0·393	0·333	111·1	344·0	243·3	100·7	0·414	0·335
25	M	34	67·7	418·5	298·7	119·8	0·401	0·354	100·0	371·4	243·0	128·4	0·528	0·407
26	M (P)	38	61·2	413·5	299·4	114·1	0·381	0·343	109·0	348·6	245·7	102·9	0·418	0·339
Mean		27·1	73·94	397·0	289·66	107·16	0·370	0·331	103·61	359·08	252·23	106·85	0·426	0·349
SEM			±1·97	±2·72 (548·29) ±3·20	±3·99 (412·41) ±3·09	±1·75 (136·73) ±1·61	±0·0071	±0·0047	±2·72	±5·79 (572·71) ±3·2	±5·09 (424·23) ±2·84	±3·26 (148·28) ±2·56	±0·0143	±0·007
Significance														

Abbreviations: HR: Heart rate; (P): right atrial pacing.
In parentheses: Corrected values for heart rate according to Weissler's regression equations.

calculated, as proposed by Weissler *et al.* (1968, 1969). The PEP was estimated by subtracting the LVET from the QS_2. All measurements were performed between 8·00 and 9·00 a.m. at the fasting state and supine position.

Paper speed was 100 mm/s. Ten to fifteen consecutive heart beats were measured to the closest 5 ms and averaged. Care was taken to start and finish measuring at the same respiratory phase, as estimated by direct observation of the patient and manual marking of the inspiration phase on the chart paper. The arterial blood pressure was measured by a cuff sphygmomanometer immediately after recording the systolic time intervals.

The nature and purpose of this study was explained to all participants and informed consent was obtained.

After the initial basal study, atropine was given intravenously in 0·5 mg increments every 3 minutes to 24 subjects, until a heart rate around 110/min or a total dose of 1·5 mg was reached. The systolic time intervals were measured at the highest rate achieved. In 2 subjects, in whom rapid right atrial pacing was performed, they were measured at basal heart rate levels and at 111·1 and 109·0 beats/min, 2 minutes after these heart rates had been reached (Table).

Before and after the production of tachycardia, the QS_2 index ($QS_{2\,I}$), PEP index (PEP_I), and LVET index ($LVET_I$) were calculated according to the regression equations of Weissler *et al.* (1969)

Males:

$QS_{2I} = QS_2 + 2{\cdot}1$ heart rate
$LVET_I = LVET + 1{\cdot}7$ heart rate
$PEP_I = PEP + 0{\cdot}4$ heart rate

Females:

$QS_{2I} = QS_2 + 2{\cdot}0$ heart rate
$LVET_I = LVET + 1{\cdot}6$ heart rate
$PEP_I = PEP + 0{\cdot}4$ heart rate

ΔHR	$\Delta PEP/LVET$	$\Delta PEP_I/LVET_I$	% $PEP/LVET$	% $PEP_I/LVET_I$	$\Delta\%$
31·1	+0·067	+0·029	+18·15	+ 8·52	9·62
6·9	+0·015	−0·099	+ 4·98	−3·13	8.11
46·6	+0·070	+0·012	+17·32	+ 3·38	13·93
51·1	+0·050	+0·014	+14·97	+ 4·54	10·42
23·4	+0·041	+0·005	+10·07	+ 1·44	8·62
37·3	+0·046	+0·014	+13·14	+ 4·34	8·79
40·8	+0·060	+0·050	+16·99	+15·77	1·21
34·2	+0·002	−0·008	+ 0·62	− 2·69	3·31
30·0	+0·155	+0·044	+40·57	+12·86	27·7
21·8	+0·078	+0·035	+20·25	+10·23	10·02
26·1	+0·080	+0·033	+21·28	+ 9·85	11·43
38·4	+0·065	+0·018	+15·66	+ 4·98	10·68
12·0	−0·017	−0·013	− 4·78	− 4·07	0·80
33·0	+0·005	−0·010	+ 1·30	− 2·90	4·20
37·7	+0·046	+0·006	+12·60	+ 1·85	10·75
18·0	+0·023	+0·011	+ 7·64	+ 3·86	3·78
22·1	+0·001	−0·005	+ 0·31	− 1·68	1·99
38·6	+0·095	+0·041	+26·31	+12·31	14·00
36·2	+0·044	+0·023	+10·67	+ 6·64	4·03
16·0	+0·045	+0·018	+10·51	+ 4·82	5·69
21·3	+0·030	+0·004	+ 8·15	+ 1·22	6·93
14·6	+0·078	+0·037	+18·22	+10·14	8·08
35·8	+0·124	+0·025	+34·73	+ 7·69	27·04
17·4	+0·021	+0·002	+ 5·34	+ 0·60	4·74
32·3	+0·127	+0·053	+31·67	+14·97	16·7
47·8	+0·037	−0·004	+ 9·71	+ 1·17	10·88
29·66 ±2·27	0·054 ±0·0078	0·016 ±0·0038	+14·08	+ 4·78	9·36 ±1·24
	P<0·001	P<0·001			P<0·001

After the PEP/LVET ratio was calculated, a $PEP_I/LVET_I$ ratio was also estimated. The values of both ratios before and after the production of tachycardia were compared by the paired t test.

The PEP/LVET and the $PEP_I/LVET_I$ ratio were correlated to heart rate either before the production of tachycardia (26 correlations), or after its production (26 correlations). Moreover, these ratios were correlated with heart rate both at rest and at tachycardia (52 correlations), by the regression analysis test.

Results

Under basal conditions the systolic time interval values in our subjects were within the accepted normal range (Table). With increase of the basal heart rate from 73·94±1·97 to 103·61±2·72/min, there was a consistent shortening of the QS_2 and LVET, while the PEP did not appreciably change. The PEP/LVET ratio increased consistently and significantly (Table, Fig. 1). The $PEP_I/LVET_I$ was also found to increase with heart rate. However, the percentage change in each patient was significantly smaller in the $PEP_I/LVET_I$ ratio than in the PEP/LVET ratio ($P<0·001$, Table).

The PEP/LVET or the $PEP_I/LVET_I$ ratio in the 26 subjects were not related to heart rate at rest ($r=0·168$, $P>0·10$, and $r=0·0143$, $P>0·10$, respectively). They were not significantly related to the heart rate after tachycardia, either ($r=0·336$, $P>0·05$ and $r=0·102$, $P>0·10$, respectively). However, when all 52 heart rate measurements (before and after tachycardia) were pooled the PEP/LVET ratio was significantly correlated to heart rate ($r0=·508$, $P<0·01$ Fig. 2).

When the $PEP_I/LVET_I$ ratio was used, there was no correlation of the 52 measurements to heart rate ($r=0·267$, $P>0·05$, Fig. 3).

From the correlation of PEP/LVET to the total of 52 heart rate measurements the following regression equation was calculated:

PEP/LVET: 0·249+0·00168 HR.

The arterial blood pressure was normal in all subjects, and did not appreciably change with the increase in heart rate.

Discussion

From our findings we cannot reach any conclusions as to whether the PEP/LVET should always be corrected for heart rate or not. However, we are puzzled by certain discrepancies in the published reports. It has been shown that the PEP is only minimally affected by changes in the heart rate (Harris *et al.*, 1967; Talley *et al.*, 1971); our findings are similar.

The PEP is significantly correlated with dP/dt max and the ejection fraction (Aronow *et al.*, 1971, McConahay *et al.*, 1972; Ahmed *et al.*, 1972); a weaker but still quite satisfactory correlation has also been found with the stroke volume (Weissler *et al.*, 1968, 1969; Ahmed *et al.*, 1972).

The stroke volume is affected considerably by tachycardia (Weissler, Peeler, and Roehll, 1961; Stein *et al.*, 1966; Benchimol and Liggett, 1966). It is probable that the PEP is prevented from lengthening during the tachycardia-induced decrease in stroke volume by a compensatory shortening through the increased contractility associated with tachycardia (Vatner and Braunwald, 1974; Schwarz, Thormann, and Winkler, 1975; Roy, Sowton, and DiLuzio, 1975).

The ejection fraction does not significantly change with tachycardia in dogs (Bristow *et al.*,

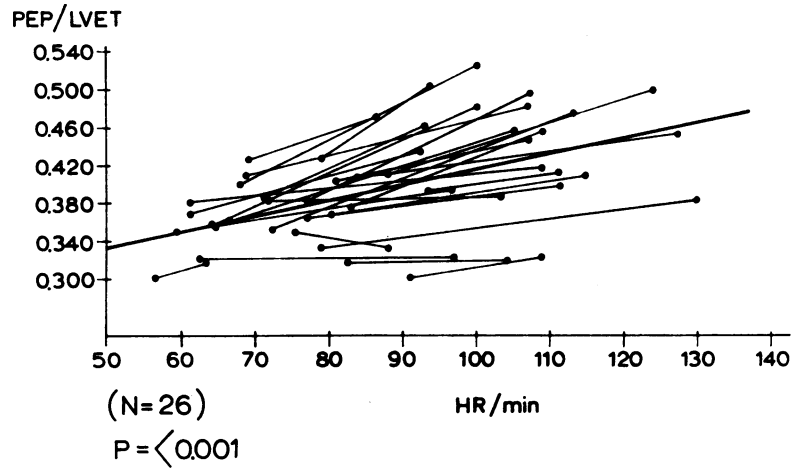

FIG. 1 *Increase of the uncorrected PEP/LVET ratio over the basal values with the occurrence tachycardia in the 26 patients used in the present study.*

1963) or humans (Krayenbuehl *et al.*, 1975).

There is agreement among the various authors about the profound effects of heart rate changes on the LVET. When rate corrected, this interval correlates well with the stroke volume and ejection fraction, but less well with the dP/dt (McConahay *et al.*, 1972).

The uncorrected PEP/LVET (and its reverse analogue, the LVET/EICT) ratio has been found to correlate better with the ejection fraction and dP/dt than the corrected LVET, PEP, or EICT alone (Garrard, Weissler, and Dodge, 1970; Aronow *et al.*, 1971; McConahay *et al.*, 1972). If this ratio is used as an expression of stroke volume, then it should probably not be rate-corrected. However, if it is taken as an index of cardiac contractility, or the ejection fraction, it should be rate-corrected, especially when serial measurements are carried out in the same individual after pharmacological or physiological interventions. Otherwise, any drug or man-

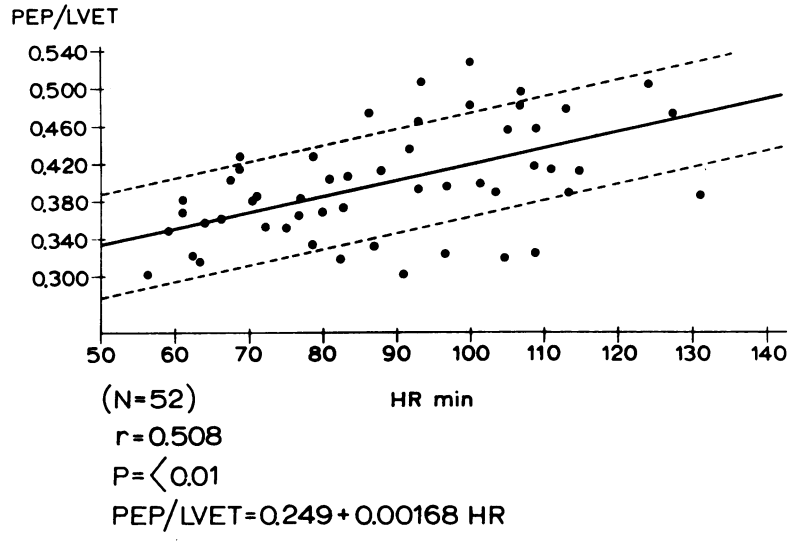

FIG. 2 *Significant correlation of the uncorrected PEP/LVET ratio with 52 heart rate measurements (26 patients, studied at basal conditions and after production of tachycardia).*

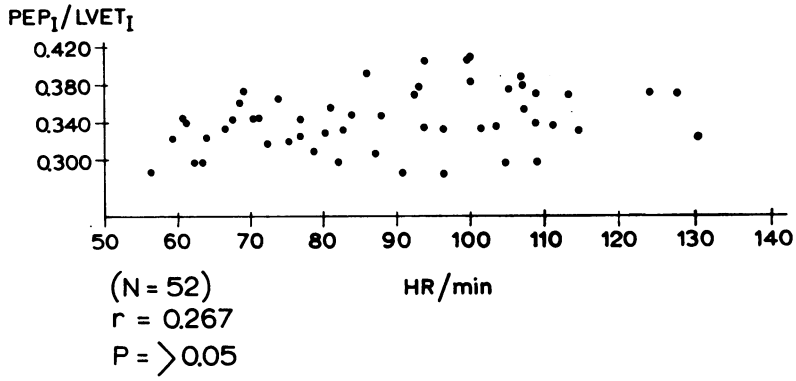

FIG. 3 *Absence of correlation of the PEP$_I$/LVET$_I$ ratio with 52 heart rate measurements. Correction of both PEP and LVET has been carried out according to Weissler's regression equations.*

oeuvre affecting increases in the HR can increase the uncorrected PEP/LVET ratio; thus a diminution of left ventricular contractility may be mistakenly suggested. Spitaels *et al.* (1974) have recently found that in normal children there is no correlation between the PEP/LVET and heart rate found under basal conditions. Our data are in complete accord with this finding. Probably, PEP/LVET values differ so much among individual patients, that the influence of heart rate does not become apparent when an individual is studied at random. Thus, in Fig. 2 it can be seen that the ratio PEP/LVET would be 0·410 at a heart rate of 70/min, and 0·380 at a heart rate of 110/min and still lie within the confidence limits, since there is a large scatter of values. However, when large groups of subjects are compared, or when the inotropic action of various interventions which also significantly affect heart rate is assessed in groups or individuals, or when single patients are studied serially, then rate correction should probably be carried out.

We do not know whether the regression equations that we propose are realistic enough. Probably individual correction for each subject would have been preferable, but our recordings of STI at intermediate heart rates during atropine infusion were too few to allow such a calculation.

We noticed that if we corrected the PEP/LVET ratio for the observed heart rate changes by simply substituting for it the PEP$_I$/LVET$_I$ ratio, according to Weissler's equations, there was still an increase of this ratio with tachycardia, as compared with the basal state (Table).

Up to the rates attained in our subjects, even this correction may still erroneously underestimate contractility.

Weissler's equations and those of Fabian, Epstein, and Coulshed (1972) were calculated from studies performed on a group of 121 men and 90 women with normal cardiac function, under basal conditions. Thus, these equations may not be appropriate for correcting the STI in serially studied individuals. On the other hand, Layton *et al.* (1973) and Lindquist, Spangler, and Blount (1973) used regression equations based on serial measurements.

In most of our subjects tachycardia was produced by atropine. This drug has been widely used to this purpose by Weissler's group (Harris *et al.*, 1967), who consider it free of any inotropic action. Similarly, Kosowsky *et al.* (1966) found no differences in the haemodynamic measurements between atropine and right atrial pacing-induced tachycardia.

We have no haemodynamic or angiographic studies to support our findings. However, such studies have been carried out in detail by others, as already discussed, and there is no reason why these data should not apply for the individuals presented in our report. It is self-evident that these conclusions are valid as long as tachycardia does not produce ischaemia, which would alter both the haemodynamic parameters and the systolic time interval values.

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